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Synthesis and Fungicidal Activity against *Pyricularia oryzae* of 6-(1,2,4-Triazol-4-yl) chromone and -1-thiochromone Derivatives‡

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Abstract: A series of novel 6-(1,2,4-triazol-4-yl) chromone and -1-thiochromone (benzo[*b*]thiazin-4-one) derivatives was obtained by cyclisation *via* thiosemicarbazides which were prepared by reaction of hydrazines and the corresponding isothiocyanates. Their fungicidal activity was evaluated against the rice blast fungus *Pyricularia oryzae*. Of this series, 2,5,8-trimethyl-6-(1-propyl-5-thioxo-3-trifluoromethyl-1,2,4-triazol-4-yl) chromone, 6-(1-butyl-5-thioxo-3-trifluoromethyl-1,2,4-triazol-4-yl)-2,5,8-trimethylchromone, 6-(1-hexyl-3-methyl-5-thioxo-1,2,4-triazol-4-yl)-2,5,8-trimethylchromone and 6-(1-allyl-5-thioxo-3-trifluoromethyl-1,2,4-triazol-4-yl)-2,5,8-trimethylchromone were highly active (pEC$_{50}$ > 6·0). Structure–activity relationship studies using the capacity factor k' as a hydrophobicity index suggested that the log k' optimum for 2,5,8-trimethylchromone and -1-thiochromone derivatives was around 1·0, equivalent to a log P_{ow} value of *c.* 4·4. © 1998 SCI

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Key words: triazolylchromone; fungicide; rice blast; *Pyricularia oryzae*

1 INTRODUCTION

Chromones are well known as natural products[1] which have fungicidal activity.[2,3] Their artificial analogs have been synthesised and found to have versatile biological activities.[4–7] However, no chromone derivatives have been developed as commercial pesticides. On the other hand, triazolyl groups are frequently used in agrochemicals.[8–11] We have synthesised, therefore, a series of chromone derivatives having a triazolyl group and evaluated their biological activities. We found that 6-(1,2,4-triazol-4-yl) chromone derivatives (Fig. 1) have potent activity against the rice blast fungus *Pyricularia oryzae* Cav. Structure–activity relationships (SARs) in the chromone and 1-thiochromone† derivatives were studied using physicochemical parameters of substituents and the capacity factor k'[12–14] as a hydrophobicity index. In this paper, synthesis, fungicidal activity and SARs of chromone and 1-thiochromone derivatives are described.

2 EXPERIMENTAL

2.1 General

Proton nuclear magnetic resonance ([^{1}H] NMR) spectra were recorded on an HR R-24B (Hitachi Corp., Tokyo, Japan), a JNM-EX90A (JEOL Ltd, Tokyo, Japan), or an Avance DPX 300 (Bruker, Karlsruhe, Germany) NMR spectrometer in deuterochloroform or hexadeuterodimethyl sulfoxide. Chemical shifts (δ) were

‡ In IUPAC nomenclature, these are referred to as [4*H*]-benzo[*b*]thiazin-4-ones, but the term 1-thiochromone is retained here for case of comparison.

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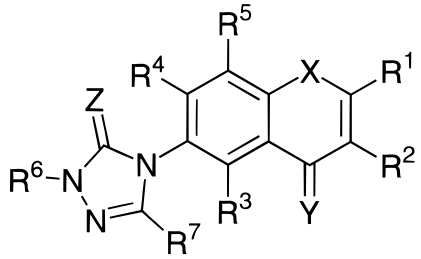


Fig. 1. General structure of 6-(1,2,4-triazol-4-yl)chromones.

in ppm relative to tetramethylsilane as the internal standard. Melting points were measured with a model MP-2 melting point apparatus (Yamato Scientific Co., Ltd, Tokyo, Japan) and were uncorrected. The compounds synthesised are shown with their melting points (m.p.) in Tables 1–6.

2.2 Synthesis

Five routes employed for the preparation of 6-nitrochromones are outlined in Figs 2–4. Chromone rings were prepared *via* route A by cyclic condensation of the corresponding phenol and β-ketoester in polyphosphoric acid[15] (Fig. 2) or by cyclisation of 2-hydroxyacetophenones obtained by acylation of phenols (Fig. 2, route B).[5,16] While chromones were usually nitrated at the 6-position, 8-methylchromone derivatives without substituents at the 5-position were prepared *via* route C (Fig. 2) because the nitration occurred at the 5-position on the chromone ring. The 5-nitro derivative was utilised as an intermediate of 5-chloro and 5-methoxy derivatives (Fig. 3, route D). The 2-methylthio derivative was prepared by methylation of 4-hydroxy-2-thio-2*H*-1-benzopyran (Fig. 4, route E).[17] Isothiocyanate derivatives were prepared by treating the corresponding amino derivatives with thiophosgene following reduction of the 6-nitro derivatives. Triazolylchromone derivatives were obtained by cyclisation *via* thiosemicarbazides prepared by reaction of hydrazines and isothiocyanates (Fig. 5). Several hydrazines were synthesised by well-known methods.[18–20] The triazol-5-one derivatives were prepared by treating the triazole-5-thiones with pyridinium chlorochromate,

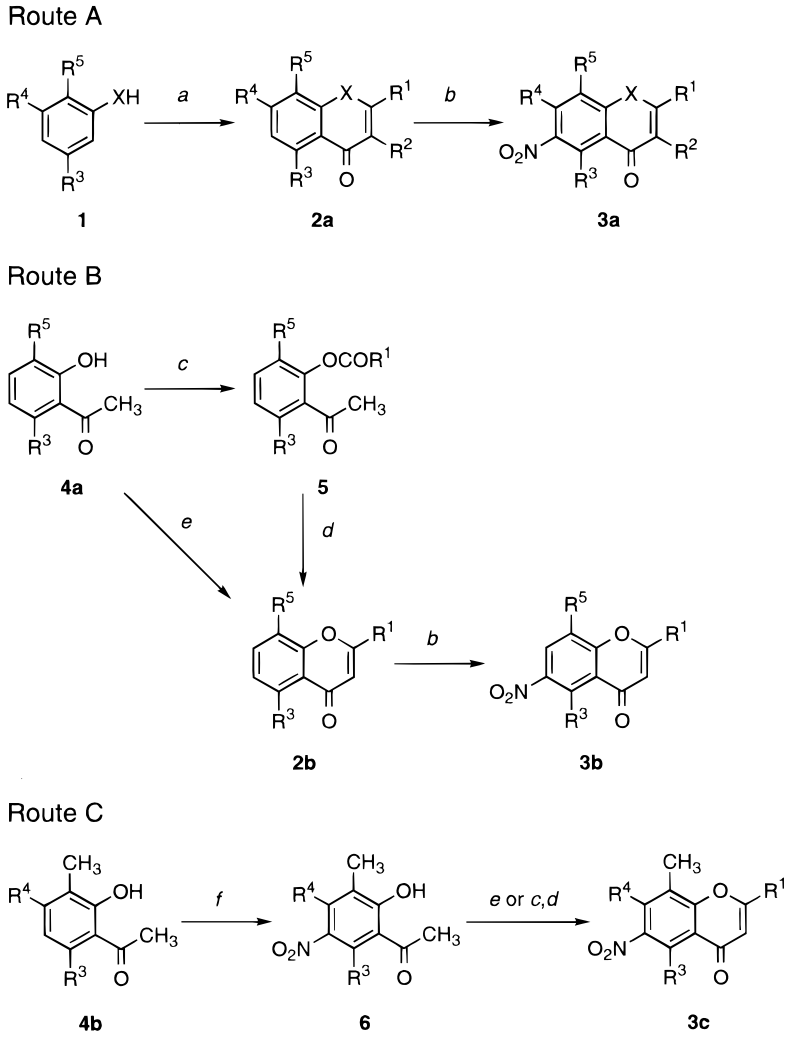


Fig. 2. Routes to 6-nitrochromones.

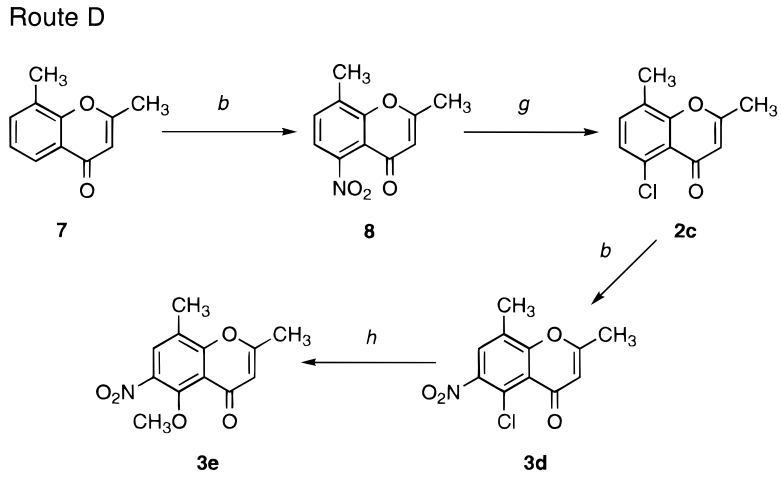


Fig. 3. Routes to 5-chloro-2,8-dimethyl-6-nitrochromone and 5-methoxy-2,8-dimethyl-6-nitrochromone.

and the 4-thioxo derivative was obtained by reaction of the corresponding 4-oxo derivative with Lawesson's reagent[21] (Wako Pure Chemical Industries Ltd, Osaka, Japan) (Fig. 6).

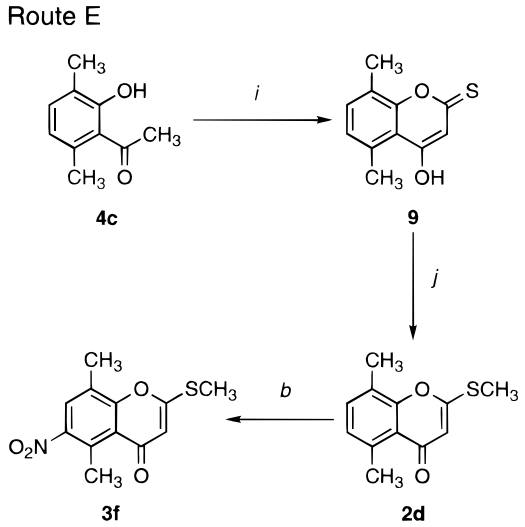


Fig. 4. Route to 5,8-dimethyl-2-methylthio-6-nitrochromone.

2.2.1 Route A (Fig. 2)

2.2.1.1 Procedure a: Synthesis of 2,5,8-trimethylchromen-4(4H)-one (Fig. 2; ***2a****;* $R^1 = R^3 = R^5 = CH_3$, $R^2 = R^4 = H$, $X = O$). To a mixture of polyphosphoric acid (500 g) and 2,5-dimethylphenol (65·1 g, 0·53 mol) was added dropwise ethyl acetoacetate (83·2 g, 0·64 mol) at 90°C, and the mixture was stirred for 1·5 h at 90°C. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residual solid was washed with hexane to afford an orange solid: 44·0 g (44%); [^{1}H]NMR ($CDCl_3$) δ: 2·35 (s, 3H), 2·40 (s, 3H), 2·80 (s, 3H), 6·08 (s, 1H), 6·98 (d, 1H, J = 7·5 Hz), 7·30 (d, 1H, J = 7·5 Hz).

2.2.1.2 Procedure b: Synthesis of 2,5,8-trimethyl-6-nitrochromen-4 (4H)-one (*Fig. 2;* ***3a****;* $R^1 = R^3 = R^5 = CH_3$, $R^2 = R^4 = H$, $X = O$). To a mixture of sulfuric acid (110 g, 1·17 mol) and nitric acid (17·7 g, 280 mmol) was added batchwise solid 2,5,8-trimethylchromen-4

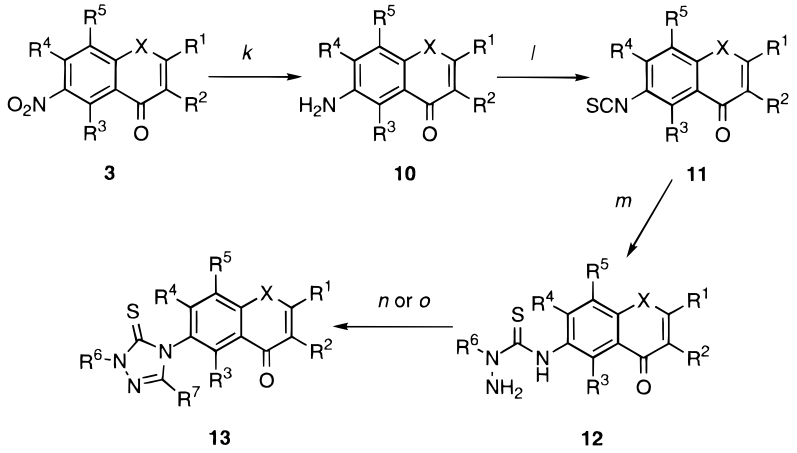


Fig. 5. Synthesis of 6-(1,2,4-triazol-4-yl)chromones.

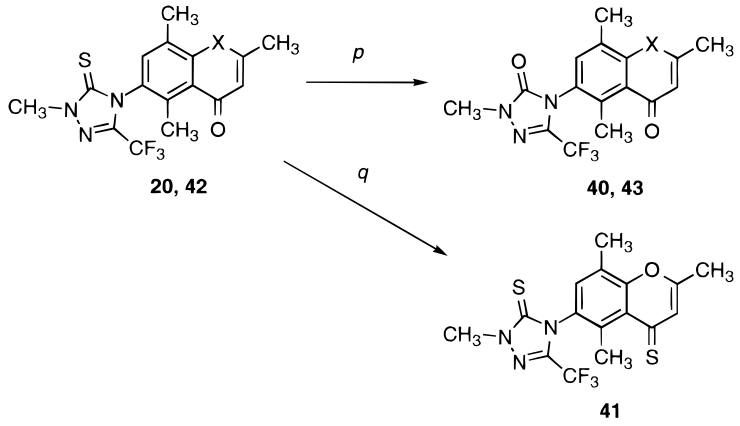


Fig. 6. Conversion of the atoms at 4- and 5′-position of 6-(1,2,4-triazol-4-yl)chromones.

(4*H*)-one **2** (44·0 g, 234 mmol) at 0°C, and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice-water and extracted with chloroform. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residual solid was washed by hexane to afford a brown solid: 42·8 g (78%); [^{1}H]NMR ($CDCl_3$) δ: 2·39 (s, 3H), 2·47 (s, 3H), 2·88 (s, 3H), 6·16 (s, 1H), 7·76 (s, 1H).

2.2.2 *Route B* (*Fig. 2*)

2.2.2.1 Procedure c: Synthesis of 2-acetyl-3,6-dimethylphenyl isobutyrate (*Fig. 2;* **5**; $R^1 = CH(CH_3)_2$, $R^3 = R^5 = CH_3$). To a mixture of 2-hydroxy-3,6-dimethylacetophenone (2·50 g, 15·2 mmol) and triethylamine (1·80 g, 18·2 mmol) in chloroform (40 ml) was added dropwise isobutyryl chloride (1·90 ml, 18·2 mmol) at 0°C, and the mixture was stirred for 8 h at room temperature. The reaction mixture was poured into water, and the layers were separated. The aqueous layer was washed with chloroform. The organic layers were combined, washed with brine, and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 4 + 1 by volume) to afford a pale yellow oil: 3·30 g (92%); [^{1}H]NMR ($CDCl_3$) δ: 1·30 (d, 6H, J = 6·9 Hz), 2·10 (s, 3H), 2·25 (s, 3H), 2·43 (s, 3H), 2·70–2·90 (m, 1H), 6·99 (d, 1H, J = 7·8 Hz), 7·13 (d, 1H, J = 7·8 Hz).

2.2.2.2 Procedure d: Synthesis of 2-isopropyl-5,8-dimethylchromen-4(4H)*-one* (*Fig. 2;* **2b**; $R^1 = CH(CH_3)_2$, $R^3 = R^5 = CH_3$). To a suspension of sodium hydride (60% in oil, 0·61 g, 15·4 mmol) in dry tetrahydrofuran (THF, 15 ml) cooled at 0°C was added a solution of 2-acetyl-3,6-dimethylphenyl isobutyrate (3·30 g, 14·0 mmol) in dry THF (15 ml), and the mixture was stirred for 30 min and then refluxed for 2 h. Dilute hydrochloric acid was added, and the layers were separated. The aqueous layer was washed with ethyl acetate. The organic layers were combined, washed with brine, and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue dissolved in toluene (50 ml) was stirred and refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate to remove water with a Dean-Stark apparatus. After 14-h reflux, the reaction mixture was concentrated under vacuum. Water was added, and the aqueous layer was washed with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 4 + 1 by volume) to afford a pale orange oil: 2·30 g (75%); [^{1}H]NMR ($CDCl_3$) δ: 1·32 (d, 6H, J = 6·8 Hz), 2·42 (s, 3H), 2·80 (s, 3H), 2·70–2·95 (m, 1H), 6·10 (s, 1H), 6·98 (d, 1H, J = 7·5 Hz), 7·30 (d, 1H, J = 7·5 Hz).

2.2.2.3 Procedure e: Synthesis of 5,8-dimethylchromen-4(4H)*-one* (*Fig. 2;* **2b**; $R^1 = H$, $R^3 = R^5 = CH_3$). To a solution of 2-hydroxy-3,6-dimethylacetophenone (1·20 g, 7·30 mmol) in xylene (20 ml) was added dropwise *N*,*N*-dimethylformamide dimethyl acetal (1·00 g, 8·40 mmol) in xylene (5 ml) at room temperature, and the mixture was stirred and refluxed overnight. The reaction mixture was evaporated, and the residue was poured into water and extracted with ethyl acetate. The extracts were washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 2 + 1 by volume) to afford a brown solid: 0·80 g (63%); [^{1}H]NMR ($CDCl_3$) δ: 2·40 (s, 3H), 2·81 (s, 3H), 6·24 (d, 1H, J = 5·8 Hz), 7·01 (d, 1H, J = 7·5 Hz), 7·32 (d, 1H, J = 7·5 Hz), 7·77 (d, 1H, J = 5·8 Hz).

2.2.3 *Route C* (*Fig. 2*)

2.2.3.1 Procedure f: Synthesis of 2-hydroxy-3-methyl-5-nitroacetophenone (*Fig. 2;* **6**; $R^3 = CH_3$, $R^4 = H$). To a

solution of 2-hydroxy-3-methylacetophenone (19·0 g, 127 mmol) in acetic acid (100 ml) was added dropwise 61% nitric acid (14·4 g, 139 mmol) at 0°C, and the mixture was stirred for 1·5 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residual solid was recrystallised from diethyl ether to afford a yellow solid: 11·5 g (46%); [^{1}H]NMR ($CDCl_3$) δ: 2·35 (s, 3H), 2·74 (s, 3H), 7·26 (s, 1H), 6·99 (d, 1H, J = 7·8 Hz), 7·13 (d, 1H, J = 7·8 Hz).

2.2.4 *Route D* (*Fig. 3*)

2.2.4.1 Procedure g: Synthesis of 5-chloro-2,8-dimethylchromen-4 (*4*H)*-one* ***2c***. A mixture of 2,8-dimethyl-5-nitrochromen-4 (4*H*)-one **8** (2·19 g, 10·0 mmol), iron powder (1·68 g, 30 mmol) in 5% acetic acid (30 ml), and ethyl acetate (15 ml) was stirred and refluxed for 1 h. The reaction mixture was diluted with 50 ml of ethyl acetate and filtered through Celite (No. 545, Wako Pure Chemical Industries Ltd, Osaka, Japan). The filtrate was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, filtered, and concentrated under vacuum to afford a brown solid. To a solution of copper (I) chloride (1·00 g, 10·0 mmol) in 28% hydrochloric acid (4·0 ml) was added dropwise a suspension of the residual solid in 28% hydrochloric acid (10 ml), and then sodium nitrite (0·56 g, 8·10 mmol) in water (1·6 ml) at 0°C, and the resulting mixture was stirred for 15 min at 0°C and 1 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum to afford a yellow solid: 0·64 g (31%); [^{1}H]NMR ($CDCl_3$) δ: 2·36 (s, 3H), 2·41 (s, 3H), 6·14 (s, 1H), 7·24 (d, 1H, J = 8·0 Hz), 7·32 (d, 1H, J = 8·0 Hz).

2.2.4.2 Procedure h: Synthesis of 5-methoxy-2,8-dimethyl-6-nitrochromen-4(*4*H)*-one* ***3e***. A mixture of 5-chloro-2,8-dimethyl-6-nitrochromen-4(4*H*)-one **3d** (1·58 g, 6·00 mmol) and 28% sodium methoxide (1·98 g, 10·0 mmol) in dry methanol (15 ml) was stirred and refluxed for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 2 + 1 by volume) to afford a pinkish solid: 0·33 g (22%); [^{1}H]NMR ($CDCl_3$) δ: 2·40 (s, 3H), 2·46 (s, 3H), 4·06 (s, 3H), 6·15 (s, 1H), 7·87 (s, 1H).

2.2.5 *Route E* (*Fig. 4*)

2.2.5.1 Procedure i: Synthesis of 4-hydroxy-5,8-dimethylchromene-2(2H)*-thione* ***9***. To a suspension of potassium *tert*-butoxide (5·90 g, 53·0 mmol) in dry benzene (50 ml) was added dropwise a mixture of 2-hydroxy-3,6-dimethylacetophenone **4c** (3·70 g, 17·1 mmol) and carbon disulfide (1·30 g, 17·7 mmol) in dry benzene (25 ml) at 0°C, and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was poured into water and neutralised with dilute hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic layer and extracts were combined, washed with saturated aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residual solid was washed by hexane to afford a yellow solid: 1·80 g (49%); [^{1}H]NMR (DMSO-d_6) δ: 2·49 (s, 3H), 2·69 (s, 3H), 6·87 (s, 1H), 6·98 (d, 1H, J = 7·5 Hz), 7·30 (d, 1H, J = 7·5 Hz), 11·70 (bs, 1H).

2.2.5.2 Procedure j: Synthesis of 5,8-dimethyl-2-methylthiochromen-4(*4*H)*-one* ***2d***. To a mixture of 4-hydroxy-5,8-dimethylchromene-2(2*H*)-thione **9** (1·80 g, 8·70 mmol) and potassium carbonate (1·30 g, 9·60 mmol) in acetonitrile (50 ml) was added dropwise iodomethane (1·50 g, 10·4 mmol) at room temperature, and the resulting mixture was refluxed for 3·5 h. The reaction mixture was filtered, and the filtrate was poured into water and extracted with ethyl acetate. The extract was washed with water and brine and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 2 + 1 by volume) to afford a pale yellow solid: 1·47 g (77%); [^{1}H]NMR ($CDCl_3$) δ: 2·40 (s, 3H), 2·55 (s, 3H), 2·80 (s, 3H), 6·15 (s, 1H), 7·00 (d, 1H, J = 7·6 Hz), 7·29 (d, 1H, J = 7·6 Hz).

2.2.6 *Synthesis of 1,2,4-triazole-5-thiones* (*Fig. 5*)

2.2.6.1 Procedure k: Synthesis of 6-amino-2,5,8-trimethylchromen-4(*4*H)*-one* (*Fig. 5;* ***10****;* $R^1 = R^3 = R^5 = CH_3$, $R^2 = R^4 = H$, $X = O$). To a solution of 2,5,8-trimethyl-6-nitrochromen-4(4*H*)-one (57·0 g, 244 mmol) and iron powder (68·2 g, 1·22 mol) in a mixture of 2-propanol (500 ml) and water (500 ml) was added dropwise concentrated hydrochloric acid (15 ml) at room temperature. The reaction mixture was refluxed for 1·5 h with stirring, diluted with ethyl acetate (500 ml) and filtered through Celite. The filtrate was extracted with ethyl acetate. The extracts were washed

with brine, dried with magnesium sulfate, filtered, and concentrated under vacuum. The residual solid was washed by hexane to afford a brown solid: 44·2 g (89%); [^{1}H]NMR ($CDCl_3$) δ: 2·31 (s, 3H), 2·36 (s, 3H), 2·69 (s, 3H), 3·64 (bs, 2H), 6·04 (s, 1H), 6·85 (s, 1H).

*2.2.6.2 Procedure l: Synthesis of 2,5,8-trimethyl-4-oxo-4*H*-chromen-6-ylisothiocyanate* (*Fig. 5;* ***11****;* $R^1 = R^3 = R^5 = CH_3$, $R^2 = R^4 = H$, $X = O$). To a mixture of 6-amino-2,5,8-trimethylchromen-4(4*H*)-one (15·0 g, 73·8 mmol) in chloroform (100 ml) and sodium carbonate (23·5 g, 221 mmol) in water (100 ml) was added dropwise thiophosgene (6·75 ml, 88·6 mmol) at room temperature, and the resulting mixture was stirred overnight. The organic layer was separated, washed with water and brine, dried with magnesium sulfate, filtered and concentrated under vacuum. The residual solid was washed with hexane to afford a brown solid: 17·3 g (95%); [^{1}H]NMR ($CDCl_3$) δ: 2·36 (s, 3H), 2·40 (s, 3H), 2·85 (s, 3H), 6·10 (s, 1H), 7·33 (s, 1H).

*2.2.6.3 Procedure m: Synthesis of 2-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)thiosemicarbazide* (*Fig. 5;* ***12****;* $R^1 = R^3 = R^5 = R^6 = CH_3$, $R^2 = R^4 = H$, $X = O$). To a solution of methylhydrazine (1·97 g, 42·8 mmol) in benzene (100 ml) was added dropwise a solution of 2,5,8-trimethyl-4-oxo-4*H*-chromen-6-ylisothiocyanate (10·0 g, 40·8 mmol) in benzene (100 ml), and the mixture was stirred for 1 h at room temperature. The product was filtered and washed with ethyl acetate. The residual solid was dried under vacuum to afford a brown solid: 11·2 g (94%); [^{1}H]NMR ($CDCl_3$) δ: 2·34 (s, 3H), 2·41 (s, 3H), 2·72 (s, 3H), 3·76 (s, 3H), 4·01 (s, 2H), 6·08 (s, 1H), 7·60 (s, 1H), 9·26 (bs, 1H).

*2.2.6.4 Procedure n: Synthesis of 4,5-dihydro-1-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)-3-trifluoromethyl-1,2,4-triazole-5(1*H*)-thione* (*Fig. 5;* ***113****;* $R^1 = R^3 = R^5 = R^6 = CH_3$, $R^2 = R^4 = H$, $R^7 = CF_3$, $X = O$). To a suspension of 2-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl) thiosemicarbazide (4·09 g, 14·6 mmol) in toluene (30 ml) was added dropwise trifluoroacetic anhydride (4·60 g, 21·9 mmol) at room temperature. The mixture was stirred for 1 h and poured into water. The resulting organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over magnesium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 2 + 1 by volume) to afford a white solid: 4·81 g (79%); [^{1}H]NMR ($CDCl_3$) δ: 2·35 (s, 3H), 2·43 (s, 3H), 2·50 (s, 3H), 3·86 (s, 3H), 6·09 (s, 1H), 7·18 (s, 1H).

*2.2.6.5 Procedure o: Synthesis of 4,5-dihydro-1,3-dimethyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)-1,2,4-triazole-5(1*H*)-thione* (*Fig. 5;* ***13****;* $R^1 = R^3 = R^5 = R^6 = R^7 = CH_3$, $R^2 = R^4 = H$, $X = O$). A suspension of 2-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl) thiosemicarbazide (0·68 g, 2·43 mmol) in triethyl orthoacetate (4·00 g, 24·3 mmol) was stirred and refluxed for 0·5 h. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 1 + 1 by volume) to afford a white solid: 0·40 g (54%); [^{1}H]NMR ($CDCl_3$) δ: 2·10 (s, 3H), 2·38 (s, 3H), 2·45 (s, 3H), 2·50 (s, 3H), 3·80 (s, 3H), 6·10 (s, 1H), 7·22 (s, 1H).

2.2.7 Conversion of the atoms (*Fig. 6*)

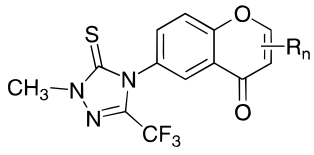
*2.2.7.1 Procedure p: Synthesis of 4,5-dihydro-1-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)-3-trifluoromethyl-1,2,4-triazol-5(1*H*)-one* (*Fig. 6;* ***40****;* $X = O$). To a suspension of pyridinium chlorochromate (5·4 g, 25 mmol) and Celite (4·0 g) in toluene (30 ml) was added dropwise a solution of 4,5-dihydro-1-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)-3-trifluoromethyl-1,2,4-triazole-5(1*H*)-thione (**20**; 1·8 g, 5·0 mmol) in toluene (20 ml), and the mixture was stirred and refluxed for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 1 + 1 by volume) to afford a white solid: 0·40 g (23%); [^{1}H]NMR ($CDCl_3$) δ: 2·36 (s, 3H), 2·43 (s, 3H), 2·57 (s, 3H), 3·59 (s, 3H), 6·10 (s, 1H), 7·23 (s, 1H).

*2.2.7.2 Procedure q: Synthesis of 4,5-dihydro-1-methyl-4-(2,5,8-trimethyl-4-thioxo-4*H*-chromen-6-yl)-3-trifluoromethyl-1,2,4-triazole-5(1*H*)-thione* (*Fig. 6;* ***41****).* A solution of 4,5-dihydro-1-methyl-4-(2,5,8-trimethyl-4-oxo-4*H*-chromen-6-yl)-3-trifluoromethyl-1,2,4-triazole-5(1*H*)-thione (**20**; 0·72 g, 2·0 mmol) and Lawesson's reagent (0·61 g, 1·5 mmol) in toluene (10 ml) was stirred and refluxed. After a 6-h reflux, the mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane + ethyl acetate, 4 + 1 by volume) to afford a dark purple solid: 0·62 g (82%); [^{1}H]NMR ($CDCl_3$) δ: 2·25 (s, 3H), 2·51 (s, 3H), 2·59 (s, 3H), 3·86 (s, 3H), 7·06 (s, 1H), 7·18 (s, 1H).

2.3 Biological test

The fungicidal activity against the rice blast fungus *P. oryzae* was evaluated as follows: Each test compound was dissolved in acetone or methanol. The solution was added to 15 ml of potato dextrose agar medium (Nissui Seiyaku Co., Ltd, Tokyo, Japan) in a test tube (15 × 180 mm) at 50°C. The final concentration of the solvent in the medium was 5 ml litre^{-1}, at which concentration no inhibition of mycelial growth was observed. The medium was poured into a plastic dish (90 × 15 mm; Nissui Seiyaku Co., Ltd, Tokyo, Japan). A mycelial disc of 5-mm diameter was placed on the medium and grown for five days at 25°C in the dark. At least two dishes were used for each concentration of a

TABLE 1
Positional Effect of the Methyl Substituents on the Chromone Ring on Fungicidal Activity against *Pyricularia oryzae*



Compound	R_n	*Synthetic route*[a]	*M.p.* (°C)	pEC_{50}[b] (±*S.E.*)
14	H	—[c]	155–156	3·56 (±0·01)
15	2-CH_3	B	156–158	3·72 (±0·03)
16	8-CH_3	C	160–162	3·71 (±0·03)
17	2,5-$(CH_3)_2$	B	148–150	4·55 (±0·02)
18	2,8-$(CH_3)_2$	C	176–177	3·97 (±0·02)
19	5,8-$(CH_3)_2$	B	209–210	4·51 (±0·06)
20	2,5,8-$(CH_3)_3$	A	134–136	5·51 (±0·05)
21	2,5,7-$(CH_3)_3$	B	176–177	ND[d]
22	2,7,8-$(CH_3)_3$	C	215–216	ND
23	2,3,5,8-$(CH_3)_4$	A	195–196	ND
ferimzone	—	—	—	5·55 (±0·11)

[a] See Section 2.1 for the synthetic routes.
[b] pEC_{50} denotes log (M required for 50% mortality)$^{-1}$; values in parentheses, standard errors.
[c] Synthesised *via* procedure *b* from chromone which is a commercial reagent.
[d] ND = Not determined.

test compound applied. The radius (mm) of the mycelial colony from the initial disc was measured, and the inhibition rate was calculated according to the equation below: Inhibition rate (%) = (1 − radius of mycelial colony on treated medium/radius of mycelial colony on untreated medium) × 100

The inhibition rates were analysed using probit analysis,[22] and the coefficients of all equations obtained were significant at $P \leq 0{\cdot}05$. A pEC_{50} value was calculated as the negative logarithm of the molar concentration required for 50% inhibition, and the values with their standard errors are listed in Tables 1–6. The commercial fungicide ferimzone ((*Z*)-2′-methylacetophenone 4,6-dimethylpyrimidin-2-ylhydrazone)[23] was used in all tests as a reference since it has been widely used for the control of the rice blast fungus *P. oryzae*.

2.4 Hydrophobicity

2.4.1 High-performance liquid chromatography (HPLC)[12–14,24]

The HPLC instruments used were composed of an L-6000 pump, a D-2500 recorder, an L-4000 UV detector, an L-5020 column oven (all from Hitachi Corp., Tokyo, Japan) and a model 7125 injector with a 200-µl loop (Rheodyne Inc., Cotati, CA, USA). Detection was done at 250 nm and a sensitivity of 4–128 mV. A Zorbax BP-ODS column (4·6 × 250 mm, Sumitomo Chemical Analysis Service Ltd, Osaka, Japan) was used at 40°C. Methanol + water (7 + 3 by volume) was used as a mobile phase, and the flow rate was 1·0 ml min^{-1}. A 10-µl sample solution (1 g litre^{-1}) was analysed, and the retention time was used to calculate the capacity factor k' as follows:

$$k' = (t_R - t_0)/t_0$$

where t_R and t_0 were the retention times of the test compound and potassium iodide, respectively. The logarithm of k' was used as a hydrophobicity index, and the values obtained are listed in Tables 5 and 6.

2.4.2 Octanol-water partition coefficient

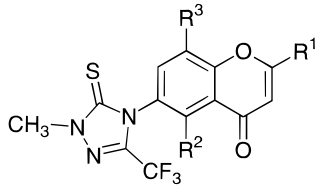
The octanol-water partition coefficient (P_{ow}) was determined by the method of Imai *et al.*[25] The HPLC instruments and the conditions were the same as in Section 2.4.1 except for the use of an Inertsil ODS-80A column (4·6 × 250 mm; GL Sciences Inc., Tokyo, Japan) and acetonitrile + water (9 + 1 by volume) as the mobile phase.

3 RESULTS AND DISCUSSION

3.1 Synthesis

In general, reaction of β-ketoesters with phenols afforded chromones. On the other hand, some target compounds were prepared from 2-hydroxyacetophenones when the desirable molecules had various substituents on the chromone ring. The 5-chloro and 5-methoxy derivatives were synthesised *via* 5-amino-2,8-dimethylchromone which was obtained by reduction of the 5-nitro derivative.

TABLE 2
Effect of 2-, 5- and 8-Substituents (R^1, R^2 and R^3) of 6-(Triazol-4-yl)chromones on Fungicidal Activity against *Pyricularia oryzae*



Compound	R^1	R^2	R^3	*Synthetic route*[a]	*M.p.* (°C)	pEC_{50} (±*S.E.*)
19	H	CH_3	CH_3	B	209–210	4·51 (±0·06)
20	CH_3	CH_3	CH_3	A	134–136	5·51 (±0·05)
24	C_2H_5	CH_3	CH_3	A	66–68	5·42 (±0·01)
25	$CH(CH_3)_2$	CH_3	CH_3	B	134–135	4·97 (±0·00)
26	C_3H_7	CH_3	CH_3	A	114–115	4·48 (±0·06)
27	C_4H_9	CH_3	CH_3	B	121–122	4·10 (±0·05)
28	CF_3	CH_3	CH_3	B	117–119	4·70 (±0·05)
29	CH_2OCH_3	CH_3	CH_3	B	108–110	4·45 (±0·02)
30	SCH_3	CH_3	CH_3	E	149–150	4·53 (±0·07)
31	CH_3	Cl	CH_3	D	180–181	5·39 (±0·01)
32	CH_3	OCH_3	CH_3	D	139–140	4·77 (±0·04)
33	CH_3	CH_3	$CH(CH_3)_2$	A	169–170	5·08 (±0·02)
34	CH_3	CH_3	Cl	B	166–167	5·49 (±0·03)
35	CH_3	Cl	Cl	B	208–209	5·34 (±0·03)

[a] See Section 2.1.

Reaction of *tert*-butylhydrazine or phenylhydrazine and the isothiocyanates did not afford the corresponding thiosemicarbazides, probably because of their bulkiness, and reaction of 2-cyclohexylthiosemicarbazide and orthoacetate was also incomplete.

3.2 Fungicidal activity

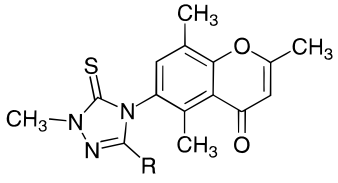
When the 1-methyl-5-thioxo-3-trifluoromethyl-1,2,4-triazol-4-yl group was attached to the 6-position of the chromone ring, the positional effect of the methyl substitution of the chromone ring on fungicidal activity against *P. oryzae* was investigated. The biological data are shown in Table 1. The 2,5,8-trimethyl derivative **20** was the most active. The others were only weakly active. The pEC_{50} values of the 2,5,7-trimethyl (**21**), 2,7,8-trimethyl (**22**) and 2,3,5,8-tetramethyl (**23**) derivatives could not be obtained because of their low water solubilities. These results suggested that the 2-, 5- and 8-substituents of the chromone ring were required for fungicidal activity.

The effect of substituents at the 2-, 5- and 8-positions of chromone derivatives was evaluated when the triazolyl group was attached to the 6-position of the chromone ring (Table 2). The 2-ethyl derivative **24** was active. The 2-phenyl derivative, which is a flavone, was inactive (data not shown). The 5-chloro (**31**), 8-chloro (**34**) and 5,8-dichloro (**35**) derivatives showed good activity, but the most active compound was the 2,5,8-trimethyl derivative **20**.

We selected the 2,5,8-trimethylchromon-6-yl group for the 4-position of the triazole ring and examined the effect of substituents at the 3-position of triazoles on the fungicidal activity (Table 3). The trifluoromethyl (**20**) and the methyl (**37**) derivatives were highly active. However, conversion of the trifluoromethyl group to hydrogen or alkyl groups decreased the activity.

The effect of atoms at the 1-, 4- and 5′-positions of the triazolylchromones was also examined (Table 4). The fungicidal activities of the 1-thiochromone deriv-

TABLE 3
Effect of 3′-Substituents (R) of 2,5,8-Trimethylchromones on Fungicidal Activity against *Pyricularia oryzae*

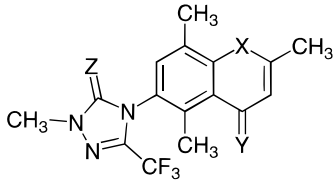


Compound[a]	*R*	*M.p.* (°C)	pEC_{50} (±*S.E.*)
20	CF_3	134–136	5·51 (±0·05)
36	H	172–173	4·37 (±0·03)
37	CH_3	175–176	5·01 (±0·06)
38	C_2H_5	100–103	4·86 (±0·05)
39	C_3H_7	168–170	4·47 (±0·00)

[a] Synthesised *via* route A.

TABLE 4

Effect of Atoms at the 1-, 4- and 5′-Positions (X, Y and Z) of 2,5,8-Trimethylchromones on Fungicidal Activity against *Pyricularia oryzae*

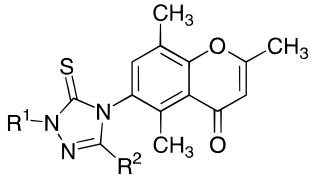


Compound	*X*	*Y*	*Z*	*Synthetic route*[a]	*M.p.* (°*C*)	pEC_{50} (± *S.E.*)
20	O	O	S	A	134–136	5·51 (±0·05)
40	O	O	O	—[b]	153–157	5·17 (±0·04)
41	O	S	S	—[c]	178 (decomposed)	5·27 (±0·04)
42	S	O	S	A	181–182	5·73 (±0·05)
43	S	O	O	—[b]	190–191	5·33 (±0·04)

[a] See Section 2.1.
[b] Synthesised *via* procedure *p*.
[c] Synthesised *via* procedure *q*.

TABLE 5

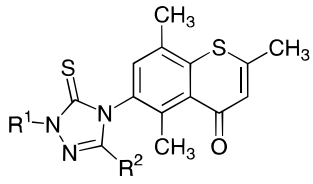
Effect of 1′- and 3′-Substituents of 2,5,8-Trimethylchromones on Fungicidal Activity against *Pyricularia oryzae*



				pEC_{50}		
Compound[a]	R^1	R^2	*M.p.* (°*C*)	*Obsd* (±*S.E.*)	*Calcd*[b]	*Log k′*[c]
20	CH_3	CF_3	134–136	5·51 (±0·05)	5·55	0·543
37	CH_3	CH_3	175–176	5·01 (±0·06)	4·70	0·078
44	C_2H_5	CF_3	78–79	5·57 (±0·01)	5·76	0·740
45	C_2H_5	CH_3	149–150	5·04 (±0·06)	5·00	0·214
46	$CH(CH_3)_2$	CF_3	161–162	5·67 (±0·03)	5·87	0·923
47	$CH(CH_3)_2$	CH_3	213–214	5·00 (±0·03)	5·28	0·361
48	C_3H_7	CF_3	143–144	6·11 (±0·03)	5·87	0·939
49	C_3H_7	CH_3	235–236	5·42 (±0·07)	5·30	0·373
50	C_4H_9	CF_3	118–119	6·08 (±0·01)	5·89	1·153
51	C_4H_9	CH_3	151–152	5·60 (±0·05)	5·57	0·560
52	C_5H_{11}	CF_3	78–79	5·87 (±0·07)	5·80	1·365
53	C_5H_{11}	CH_3	129–130	5·85 (±0·07)	5·77	0·753
54	C_6H_{13}	CF_3	87–88	5·64 (±0·05)	5·60	1·582
55	C_6H_{13}	CH_3	109–110	6·25 (±0·02)	5·88	0·959
56	$CH_2CH=CH_2$	CF_3	103–104	6·15 (±0·01)	5·79	0·783
57	$CH_2CH=CH_2$	CH_3	167–168	5·18 (±0·12)	5·07	0·247
58	$CH_2C_6H_5$	CF_3	143–144	6·00 (±0·08)	5·90	1·099
59	$CH_2C_6H_5$	CH_3	174–175	5·73 (±0·08)	5·54	0·534
60	Cyclohexyl	CF_3	170–172	5·67 (±0·03)	5·77	1·408

[a] Synthesised *via* route A.
[b] From eqn (3).
[c] Log (capacity factor k′) (see Section 2.4.1 for hydrophobicity).

TABLE 6
Effect of 1′- and 3′-Substituents of 2,5,8-Trimethyl-1-thiochromones on Fungicidal Activity against *Pyricularia oryzae*



Compound[a]	R^1	R^2	*M.p.* (°C)	pEC_{50} *Obsd* (±*S.E.*)	pEC_{50} *Calcd*[b]	*Log k′*
42	CH_3	CF_3	181–182	5·73 (±0·05)	5·73	0·704
61	CH_3	CH_3	236–237	4·83 (±0·05)	5·02	0·225
62	C_2H_5	CF_3	158–159	5·67 (±0·02)	5·86	0·900
63	C_2H_5	CH_3	169–170	5·06 (±0·04)	5·29	0·365
64	$CH(CH_3)_2$	CF_3	142–143	5·61 (±0·07)	5·90	1·082
65	$CH(CH_3)_2$	CH_3	175–176	5·10 (±0·07)	5·51	0·513
66	C_3H_7	CF_3	138–139	5·88 (±0·03)	5·90	1·099
67	C_3H_7	CH_3	151–152	5·55 (±0·02)	5·53	0·526
68	C_4H_9	CF_3	153–154	5·86 (±0·00)	5·83	1·314
69	C_4H_9	CH_3	139–140	5·84 (±0·02)	5·74	0·715
70	$CH_2CH=CH_2$	CF_3	150–151	5·97 (±0·02)	5·87	0·945
71	$CH_2CH=CH_2$	CH_3	146–148	5·24 (±0·02)	5·35	0·401
72	$CH_2C_6H_5$	CF_3	178–179	5·52 (±0·00)	5·86	1·262
73	$CH_2C_6H_5$	CH_3	171–172	5·80 (±0·04)	5·72	0·692

[a] Synthesised *via* route A.
[b] From eqn (3).

atives **42** and **43** were almost equal to those of the corresponding chromone derivatives **20** and **40**, respectively. However, the 4-thioxo derivative **41** was less active than compound **20**.

The influence of substituents at the 1-position of triazoles on the activity was examined. A regression analysis was performed on the activities of the chromone derivatives **20**, **37** and **44–60** (Table 5), using log k' values and the physicochemical parameters of substituents such as Verloop's STERIMOL L, B_1 and B_4 [26] and electronic F and R,[27] and eqn (1) was obtained at the 95% confidence level.

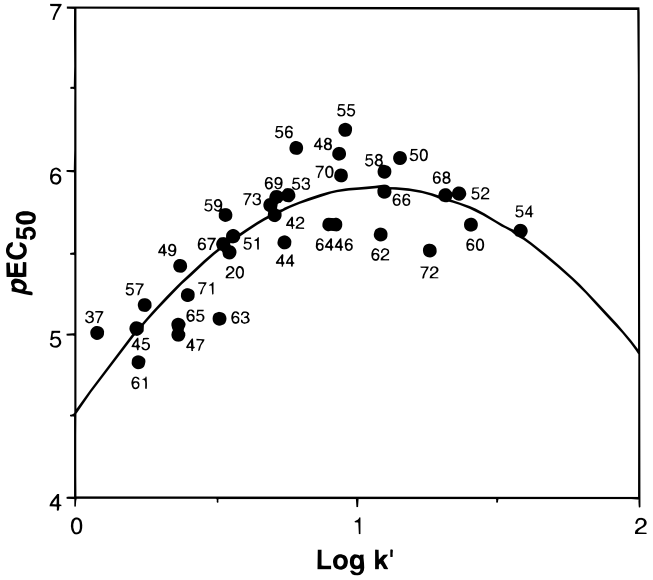


Fig. 7. Log k' versus $p\mathrm{EC}_{50}$ of 6-(5-thioxo-1,2,4-triazol-4-yl) chromones and -1-thiochromones.

$$p\mathrm{EC}_{50} = -1{\cdot}201\ (\pm 0.521) \times (\log k')^2 + 2.572\ (\pm 0.879) \times (\log k') + 4.590\ (\pm 0.323)$$
$$n = 19,\ r = 0.884,\ s = 0.193 \text{ and } F_{2,16} = 28.567 \quad (1)$$

In eqn (1) and following equations, n is the number of the compounds used, r is the correlation coefficient, s is the standard deviation and $F_{m,n-m-1}$ is the F ratio, where m is the number of independent variables. The values in parentheses are the 95% confidence intervals. Equation (1) indicates that the activity is correlated with log k', yielding a log k' optimum of 1·07. The 3-methyl-1-hexyl derivative **55** showed the highest activity ($p\mathrm{EC}_{50}$ = 6·25), having a log k' value of 0·959.

A regression analysis was done on the 1-thiochromone derivatives **42** and **61–73** (Table 6), and eqn (2) was obtained.

$$p\mathrm{EC}_{50} = -1.777\ (\pm 1.012) \times (\log k')^2 + 3.540\ (\pm 1.620) \times (\log k') + 4.071\ (\pm 0.575)$$
$$n = 14,\ r = 0.893,\ s = 0.173 \text{ and } F_{2,11} = 21.703 \quad (2)$$

Equation (2) correlates the activity and the hydrophobicity, yielding a log k' optimum of 0·996. The 1-allyl-3-trifluoromethyl derivative **70** was the most active compound ($p\mathrm{EC}_{50} = 5{\cdot}97$) among the 1-thiochromones, having a log k' value of 0·945, near the optimum 0·996.

Equations (1) and (2) indicated that the activity was dominated by hydrophobicity. The data shown in Tables 5 and 6 provided eqn (3).

$$p\mathrm{EC}_{50} = -1.192\ (\pm 0.465) \times (\log k')^2 + 2.578\ (\pm 0.772) \times (\log k') + 4.503\ (\pm 0.284)$$
$$n = 33,\ r = 0.850,\ s = 0.203 \text{ and } F_{2,30} = 38.933 \quad (3)$$

Equation (3) exhibits a parabolic relation of the activity with log k' (Fig. 7), of which the optimum is 1·08. The $p\mathrm{EC}_{50}$ values calculated by eqn (3) are shown in Tables 5 and 6.

In conclusion, hydrophobicity was suggested to be the most important factor for the fungicidal activity of the chromone and 1-thiochromone derivatives examined. The optimum log k' value of the chromone and 1-thiochromone derivatives was around 1·0, equivalent to *c.* 4·4 for log P_{ow} estimated by the calibration curve obtained from compounds **20** (0·543, 3·26), **24** (0·741, 3·78), **31** (0·366, 2·93), **33** (0·874, 3·97), **34** (0·690, 3·57), **36** (0·016, 1·66), **37** (0·078, 1·77), **39** (0·394, 2·79), **40** (0·373, 2·41), **44** (0·740, 3·73), **45** (0·214, 2·27) and **46** (0·923, 4·15) (the values in parentheses denote log k' and log P_{ow} respectively). The most active compound in this series was 6-(1-hexyl-3-methyl-5-thioxo-1,2,4-triazol-4-yl)-2,5,8-trimethylchromone ($p\mathrm{EC}_{50} = 6{\cdot}25$), having a log k' value of 0·959, and this compound was significantly more active than the commercial fungicide ferimzone ($p\mathrm{EC}_{50} = 5{\cdot}55$).

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